tematic investigations of anions.

Note Added in Proof: The rotational barriers in the anions from acetaldehyde, CH_2CHO^-, and from nitromethane, $CH_2NO_2^-$, are large, 40 and 44 kcal/mol, respectively. The calculated proton affinities of F^- and OH^- are improved when d orbitals as well as diffuse functions are included in the basis set. The PA's are, respectively, 373.6 and 401.1 kcal/mol at 6-31+G*/4-31+G and 387.1 and 362.0 kcal/mol at MP2/6-31+G*//4-31+G. We thank G. W. Spitznagel and T. Clark for this data.

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Supplementary Material Available: Calculated geometries (Table 3) and energies of neutral molecules (Table 4) (4 pages). Ordering information is given on any current masthead page.

Thermodynamic Stability of Carbonyl Anions, R—C⁻=O. A Molecular Orbital Examination

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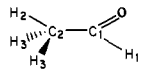
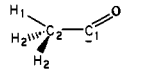
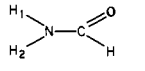
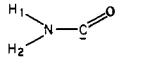
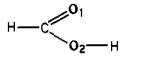
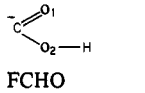
Carbonyl anions, R-C̄=O (**1**), are generally inaccessible as practical synthetic intermediates. Consequently, many carbonyl anion "synthons" have been devised in order to achieve indirectly transformations like eq 1.[1] Carbonyl anions (as metalated de-

$$\underset{\mathbf{1}}{\text{R-C}^-\!=\!\text{O}} + \text{R'X} \rightarrow \text{RR'C}\!=\!\text{O} + \text{X}^- \qquad (1)$$

rivatives) are involved in the reaction of carbon monoxide with organolithium and Grignard reagents, but the variety of products often obtained indicate the high reactivity and kinetic instability to be expected of RCOLi or RCOMgX species.[2] There is evidence for the transient formation of C^-OOR and C^-ONR_2 in solution,[3] $LiCONR_2$ and $LiCONRNR'_2$ reagents are useful synthetically.[4] In the gas phase, $ClCO^-$ dissociates readily into CO and Cl^-,[5] reactions of various bases (B^-) with formate esters, which might have given (C^-OOR, led to $ROHB^-$ and CO instead,[6] and the formyl anion, HCO^-, can be observed,[7] but appears to be only marginally stable toward both electron and CO loss (see below). The benzoyl anion, $C_6H_5CO^-$, has been generated in the gas phase recently,[8] and proton abstraction from CH_2=$CHCHO$[9] as well as from $(CH_3)_3CCHO$[10] has been investigated.

To what extent are carbonyl anions *thermodynamically* unstable? The normal polarization of carbonyl groups (**2**) and the ease of formation and the thermodynamic stability of carbonyl

Table I. 4-31+G Calculated Geometries of Carbonyl Systems[a]

HCO^-	CO = 1.254; CH = 1.166; ∠HCO = 110.0
H_2CO	CO = 1.209; CH = 1.080; ∠HCO = 121.6
	CC = 1.493; CO = 1.212; C_2H_2 = 1.079; C_2H_3 = 1.085; C_1H_1 = 1.084; ∠CCO = 124.2; $\angle C_1C_2H_2$ = 110.6; $\angle C_1C_2H_{33}$ = 125.4;[b] $\angle H_3C_2H_3$ = 107.2; $\angle C_2C_1H_1$ = 116.3
	CC = 1.574; CO = 1.250; C_2H_1 = 1.093; C_2H_2 = 1.088; ∠CCO = 113.1; $\angle C_1C_2H_1$ = 112.2; $\angle C_1C_2H_{22}$ = 122.5;[b] $\angle H_2C_2H_2$ = 107.5
	CO = 1.219; CN = 1.346; CH = 1.080; NH_1 = 0.993; NH_2 = 0.990; ∠NCO = 124.6; ∠OCH = 121.3; $\angle CNH_1$ = 119.7; $\angle CNH_2$ = 121.8
	CO = 1.261; CN = 1.414; NH_1 = 1.003; NH_2 = 0.989; ∠NCO = 113.0; $\angle CNH_1$ = 120.8; $\angle CNH_2$ = 119.8
	CO_1 = 1.203; CO_2 = 1.341; CH = 1.071; OH = 0.957; $\angle HCO_1$ = 125.1; $\angle CO_2H$ = 115.2; $\angle HCO_2$ = 110.7
	CO_1 = 1.235; CO_2 = 1.484; OH = 0.964; ∠OCO = 110.3; ∠COH = 110.0
FCHO	CF = 1.361; CO = 1.179; CH = 1.070; ∠FCO = 122.0; ∠HCO = 110.0
FCO^-	CF = 1.830; CO = 1.168; ∠FCO = 106.2

[a] Bond lengths in Å, angles in deg. See footnote 18. [b] CH_{aa} denotes the bisector of H_aCH_a angle.

Table II. Calculated Ab Initio Energies of Carbonyl Systems[a]

	4-31+G[b]		MP2/4-31+G//4-31+G[b]	
system	*E*	rel *E*	*E*	rel *E*
HCO^-	−113.05364		−113.27932	
H_2CO	−113.69766		−113.91974	
CH_3CHO	−152.69253		−153.00515	
CH_3CO^-	−152.04848	0.0	−152.37054	0.0
CH_2CHO^-	−152.09251	−27.6	−152.41432	−27.5
NH_2CHO	−168.69064		−169.02031	
NH_2CO^-	−168.05383	0.0	−168.39241	0.0
$NHCHO^-$	−168.09140	−23.6	−168.43674	−27.8
HCOOH	−188.48375		−188.82960	
$OCOH^-$	−187.87250	0.0	−188.22669	0.0
HCO_2^-	−187.92750	−34.5	−188.28706	−37.9
FCHO	−212.45367		−212.80355	
FCO^-	−211.88137		−212.24046	

[a] Total energies in hartrees, relative energies in kcal/mol. [b] Diffuse orbital exponents 0.04 added to *all* non-hydrogen atoms. See footnote 18.

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Table III. Proton Affinities (PA), Decarbonylation Energies (DE), and MNDO Heats of Formation (ΔH_f°) of Carbonyl Anions[a]

	MNDO		4-31+G		MP2/4-31+G//4-31+G	
anion	ΔH_f°	PA[b]	PA	DE[c]	PA	DE[c]
HCO^-	4.8	404.8	404.1	5.5[d]	401.9	4.2[d]
CH_3CO^-	−11.1	398.3	404.1	25.2	398.2	20.3
NH_2CO^-	−23.3	383.6	399.6	34.1	394.0	23.8
$HOCO^-$	−83.4	376.3	383.6	20.7	378.3	10.5
FCO^-	−89.1	366.1	359.1	12.9	353.3	9.1
CH_3OCO^-	−80.4	372.1				
$(CH_3)_2NCO^-$	−27.3	379.6				
$(CH_3)_3CCO^-$	−25.5	389.6				
$PhCO^-$	−3.0	373.7				
H_2CCHCO^-	6.9	392.4				

[a] All values in kcal/mol. [b] MNDO heats of formation for neutral molecules taken from ref 12. ΔH_f° of the proton was assumed to be 367 kcal/mol. [c] Energy required for the loss of CO from the RCO^- species. The MNDO values for this process are unreliable since the MNDO heats of formation for CO and for the smaller R^- ions are in error by large amounts. [d] H^- was calculated with a diffuse s function (exponent 0.04).

(acyl) *cations* (**3**),[11] suggests that the negative charge on carbon in **1** might not be favorable.[12] However, a carbonyl anion should

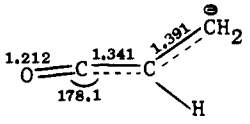
$$\underset{\mathbf{2}}{R_2C^+-O^-} \quad \underset{\mathbf{3}}{R\text{-}C^+=O} \quad \underset{\mathbf{4}}{H_2C=C^--OR}$$

be stabilized by the sp^2 hybridization and the inductive effect of the neighboring electronegative oxygen atom.[13] "Dipole stabilized" aions[1c] like **4**,[13a] which can easily be generated by lithiation,[14] are analogous sp^2 hybridized species with a neighboring oxygen atom. Resonance, $R-C^-=O \leftrightarrow R\text{-}C\text{-}O^-$, might also contribute to the stability of **1**; (possible carbene) structures like RR'NC–O–Li have been suggested.[3c,d]

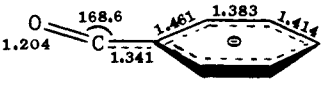
We have now examined a number of $R-C^-=O$ species, e.g., with R = H, CH_3, $(CH_3)_3C$, C_6H_5, C_2H_3, OH, OCH_3, NH_2, $N(CH_3)_2$, and F, by means of semiempirical MNDO[15] and ab initio[16] molecular orbital calculations with complete geometry optimization. Diffuse orbitals are needed for a proper ab initio description of carbanions.[17,18] Hence, we employed a newly developed 4-31+G basis[18] (the standard 4-31G basis[16] augmented by a set of diffuse s and p valence orbitals (exponents 0.04)[18] on all first-row atoms). Geometry optimization of anionic and the corresponding neutral (protonated) species (4-31+G//4-31+G) were carried out by using analytically evaluated gradients.[19] The geometries resulting (Table I) were then used for single-point assessments of the effects of electron correlation (MP2/4-31+G//4-31+G) (Table II).[20] The performance of these theoretical models with anions is very good. When zero-point corrections (usually ±5–10 kcal/mol) are taken into account, the calculated 4-31+G proton affinities are in excellent agreement with experiment.[18] MNDO proton affinities are also reasonably accurate, and the modest computer time required by thiis method make it ideal for the study of larger carbanions.[15b]

The formyl anion, $HC^-=O$, has been generated in the gas phase[7] by proton abstraction from formaldehyde by NH_2^- (proton affinity 399.6 ± 3.6 kcal/mol);[21] $C_2H_5NH^-$ (4.3 kcal/mol weaker as a base)[22] is unreactive. The calculated proton affinities (Table III) are in reasonable agreement with the experimental range (395–400 kcal/mol). On this basis, $\Delta H_f^\circ(HC^-O)$ = 2–7 kcal/mol (the MNDO value is 4.8); the electron affinity of HCO (ΔH_f° = 9 ± 2 kcal/mol)[23] is 4 ± 4 kcal/mol. The hydride affinity of CO is calculated directly (4-31+G) to be 4.2 kcal/mol (Table III); the experimental range is 1–6 kcal/mol. For comparison, the hydride affinity of acetylene is calculated to be 16 kcal/mol.[24] While the formyl anion is thus indicated to be only marginally stable toward loss of CO, the substituted carbonyl anions (Table III) (especially with carbon or amino groups) are more favorable in this respect. This agrees with chemical experience.[1-6]

The calculated geometry (4-31+G, Table I) of the formyl anion is classical, with a somewhat elongated C=O double bond (1.254 vs 1.209 Å in formaldehyde) and <HCO = 110.0°; the C—H bond (1.166 Å) is also somewhat long, reflecting its weak character. These features are found generally; the C=O and R—C bonds in nearly all anions calculated are longer than in their neutral counterparts. The $R^-\cdots CO$ character of these species are also indicated by the calculated charge distributions. $H_2C=C-HC^-O$ (**5**) and $C_6H_5CO^-$ (**6**) are exceptions. Due to acceptor stabilization, C=C double bonds are found (MNDO) between the CO group and the phenyl or vinyl substituents. The CCO groupings are nearly linear.



5, C_s [MNDO]



6, C_s [MNDO]

Formaldehyde is a stronger acid than ethylene (PA = 418 kcal/mol)[18] but is weaker than acetylene (PA = 375 kcal/mol).[21] FCOH is calculated (PA = 353 kcal/mol, 4-31+G) to be the strongest acid in the carbonyl anion series; in the absence of solvation it should be comparable to mercaptans, cyclopentadiene, and phenol in acidity.[21] The energies of isomers in Table II confirms the expected; the formate anion $HCOO^-$ is about 35 kcal/mol lower in energy than $HOOC^-$. Proton loss from the methyl groups of acetaldehyde is 28 kcal/mol more favorable than from the aldehyde group. In agreement with an assumed experimental interpretation,[9] the conjugated vinyl proton in acrolein (CH_2=CHCHO) is removed by base in preference to loss of the formaldehyde proton (which would lead to **5**).[25] Our calculated (389.6 kcal/mol) MNDO PA for $(CH_3)_3CCO^-$ is also in agreement with the experimental range (379.2–390.8 kcal/mol).[10]

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(25) The MNDO PA's for CH_2=C(CH_3)CHO, 378.3, 386.2, and ca. 400 kcal/mol for the methyl, formyl, and either of the methylene protons, respectively, are in agreement with experimental observations; CH_2=C(C-D_3)CHO undergoes 77–80% dedueteration and 20–23% formyl deprotonation with different bases in the gas phase. (Nibbering, N. M. M., private communication).

However, the $C_5H_9O^-$ anion derived from $(CH_3)_3CCHO$ exchanged only *eight* (not nine) hydrogens for deuterium; a dipole-stablized open $CH_2^-(CH_3)_2CCHO$ structure has been proposed as an explanation for this behavior.[10] Our model calculations indicate that homoenolization to give a ring-closed cyclopropoxide intermediate should be most favorable;[26] this probably is the structure of the $C_5H_9O^-$ species observed.[10] The homoenolization complication might be circumvented by the use of bridgehead-substituted tertiary aldehydes, e.g., 1-adamantyl or 1-norbornylcarboxaldehyde. We conclude that such bridgehead aldehydes, aromatic aldehydes,[8] and disubstituted formamides should be best suited for experimental studies of proton abstraction from CHO groups. We also have calculated the lithiated forms, RCOLi, of these species. The results will be reported subsequently.

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(26) For example, the cyclopropoxide anion is calculated to be about 5 kcal/mol more stable than CH_3CH_2—C=O both at 4-31+G//3-21G and MNDO levels. Chandrasekhar, J.; Andrade, J. G.; Schleyer, P. v. R., to be published.

Stereochemistry of Ribostamycin Biosynthesis. An Application of ^2H NMR Spectroscopy

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In the last several years, much attention has been paid to the biosynthesis of antibiotics, and among those being actively investigated are aminocyclitol antibiotics[1] and meta-C-C_6-N antibiotics.[2,3] In the field of the aminocyclitol antibiotics, most of the work was focused on the biosynthesis of 2-deoxystreptamine (DOS) using idiotrophs of the producing microorganisms, resulting in identification of the biosynthetic intermediates 2-deoxy-*scyllo*-inosose and 2-deoxy-*scyllo*-inosamine.[4-7] However, few stereochemical and mechanistic results have been obtained so far.

This communication deals with our studies on the biosynthesis of ribostamycin (**1**), one of the DOS-containing antibiotics, to solve the stereochemistry of DOS and neosamine C formations by means of ^2H NMR spectroscopy.

We prepared two kinds of deuterium labeled D-glucose for the feeding experiments. Thus, D-[6,6-$^2H_2$]-glucose (**2**) was synthesized by reduction of 1,2-*O*-isopropylidene-α-D-glucofuranulono-6,3-lactone with NaB^2H_4, followed by acid hydrolysis. (*6S*)-D-[6-^2H]-glucose (**3**) was prepared by a totally chemical method which we developed recently.[8]

Each labeled D-glucose was separately supplemented to the growing broth of *Streptomyces ribosidificus*, a ribostamycin producer, and each labeled antibiotic was isolated from the fermentation as usual.[9] The ^2H NMR spectra of these labeled **1** samples were measured at 61.48 MHz and are shown in Figure 1.

The spectrum A of labeled **1** derived from **2** displayed signals at δ 1.3, 2.1, 3.3, and 3.9, and their intensities were approximately 1:1:1:2. The first two signals were, respectively, assigned to the axial and equatorial hydrogens of the C-2 methylene group of DOS, on the basis of ^1H NMR chemical shifts. The third signal was due to a C-6 aminomethyl hydrogen of neosamine C, and the last signal was assigned to the hydroxymethyl group of the D-ribose moiety. Only two signals were observed in the spectrum B of labeled **1** derived from **3**, and those were assigned to the equatorial hydrogen on C-2 of DOS and a hydrogen of the hydroxymethyl group of the D-ribose moiety.

The labeling pattern of the D-ribose moiety is reasonable, because it is well established that this moiety is formed in part from the hexose monophosphate pathway.[1]

Concerning the neosamine C formation, it was clearly shown that the pro-*S* hydrogen of the hydroxymethyl group of D-glucose is stereospecifically removed during the introduction of the C-6 amino group. This implies that stereospecific dehydrogenation of D-glucosamine, which is a precursor of neosamine C,[1] takes place to give a D-glucos-6-ulosamine-type intermediate **4**, which in turn is transaminated to neosamine C with an accompanying hydrogen uptake from the medium, presumably in a stereospecific manner, as depicted in Figure 2. Mechanisms involving a substitution reaction can be ruled out. This is believed to be the first evidence suggesting the possibility of a 6-ulose-type intermediate. The stereochemistry of the transamination step is still under investigation.

The observation that both of the C-2 methylene hydrogens of DOS were equally labeled from **2** and the equatorial hydrogen was derived from the pro-*S* hydrogen of the hydroxymethyl group of D-glucose clearly indicates that no hydrogen removal has taken place at the C-6 position of D-glucose during the stereospecific cyclization of D-glucose to 2-deoxy-*scyllo*-inosose; the overall reaction proceeds with retention of configuration as shown in Figure 2. These results confirmed that the DOS biosynthesis is apparently different from the *myo*-inositol formation and hence from the biosynthesis of streptamine and actinamine.[1,10]

The overall reaction from D-glucose to 2-deoxy-*scyllo*-inosose seems to be a dehydration–condensation sequence, and a plausible mechanism is to form a hypothetical enol intermediate **5** by a lyase-like reaction, followed by subsequent attack of the nucleophilic C-6 to the C-1 aldehyde group to give the first cyclized product, 2-deoxy-*scyllo*-inosose, as suggested by Rinehart (Scheme I).[11] One may then point out the close similarity of this cyclization

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